

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/14329 A1(51) International Patent Classification⁷: C07F 9/12, (74) Agents: MORGAN, David, J. et al.; Langner Parry, 52-54 A61K 31/661, A61P 35/00 High Holborn, London WC1V 6RR (GB).

(21) International Application Number: PCT/GB01/03668

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(22) International Filing Date: 15 August 2001 (15.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0019944.8 15 August 2000 (15.08.2000) GB

(71) Applicant (for all designated States except US): ANGIOGENE PHARMACEUTICALS LTD. [GB/GB]; 14 Plowden Park, Aston Rowant, Watlington, Oxfordshire OX9 5SX (GB).

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

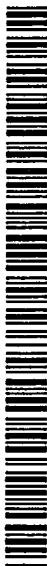
Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(72) Inventor; and

(75) Inventor/Applicant (for US only): DAVIS, Peter, David [GB/GB]; 10 Aston Park, Aston Rowant, Watlington OX9 5SX (GB).



WO 02/14329 A1

(54) Title: COMPOSITIONS WITH VASCULAR DAMAGING ACTIVITY

(57) Abstract: Compositions for the inhibition of the formation of new vacuature by angiogenesis are provided as in compounds which are salts comprising as an acidic component a compound of formula (1) wherein: R¹, R² and R³ are each independently alkyl, R⁴ is alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl, hydroxy or halo, R⁵ is hydrogen, alkoxy, alkyl, alkylthio, hydroxy, phosphate or halo, and, as the basic component, a compound selected from the group consisting of (2) a compound of formula (2) wherein R⁶ is hydrogen or alkyl R⁷ is alkyl, alkylamino, dialkylamino, nitroamino, hydrazine, mercapto or alkylthio X is CH₂, CH₂CH₂, CH₂S, CH₂CH₂S Y is NH or S or a compound of formula (3) wherein R⁸ is alkyl or aminoalkyl R⁹ is hydrogen, alkyl or optionally substituted phenyl or, a compound of formula (4) wherein Z is O, S, CH₂, CHR¹³ or a bond R¹⁰, R¹¹, R¹² and R¹³ are each independently alkyl or hydrogen or, a compound of formula (5) wherein R¹⁴ is alkyl and the pharmaceutically acceptable solvates and hydrates thereof.

COMPOSITIONS WITH VASCULAR DAMAGING ACTIVITY

The present invention relates to compounds for the treatments of diseases involving active angiogenesis and which are new vascular damaging agents.

5

Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763 (1995)). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is 10 mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy. In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is 15 expected to have a beneficial therapeutic effect.

Compounds able to damage neovasculature have advantages in the treatment of disease. For example, attacking tumour vasculature has several important advantages over a direct attack on the tumour. In particular the endothelial cells of tumour 20 vasculature are more genetically stable than those of the tumour itself and are therefore less likely to become resistant to the damaging agent. Thus a major problem in conventional anti-tumour chemotherapy, that of drug resistance, is circumvented by this approach. Furthermore, since the endothelial cells of the tumour vasculature, unlike the tumour cells themselves, are similar between different solid tumour types, 25 vascular damaging agents are able to attack a wide range of tumour types.

Certain chemical compounds have been shown to have vascular damaging activity against the newly formed endothelium of solid tumours. These agents include, for example, combretastatin A1 and combretastatin A4 (D. J. Chaplin *et al.*, British J. 30 Cancer 27, S86-S88, 1996), combretastatin A4 phosphate (Dark *et al.*, Cancer Research 57, 1829-1834, 1997), combretastatin A1 phosphate (Holwell *et al.* Proc. Amer. Assoc. Cancer Res. 41, 1363, 2000), AC7700 (Hori *et al.* Jpn. J. Cancer Res.

90, 1026-1038, 1999), colchinol derivatives (Davis *et al.*, WO 98/01977 and Davis *et al.* WO00/40529), benzimidazole derivatives (Davis, WO00/41669), the flavone acetic acids, for example 5,6-dimethylxanthenone acetic acid (Zwi, *Pathology*, 26, 161-9, 1994) and colchicine (Baguley *et al.* *Eur J Cancer* 27, 482-7, 1991). However some 5 tumours are relatively resistant to these agents. The combination of a vascular damaging agent and inhibitors of the formation or action of nitric oxide in a mammalian system have proved to be superior in some instances (Angiogene Pharmaceuticals Limited WO 00/48591).

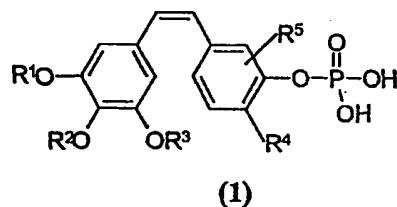
10 Tozer *et al* (*Cancer Research* 59, 1626-1634, 1999) have described the activity of combretastatin A4 phosphate in the rat P22 tumour model, which is sensitive to this agent. These authors also demonstrated an enhancing effect of L-NAME on the activity of combretastatin A4 phosphate and ascribed the enhancement to inhibition of nitric oxide production. However it is not apparent from these studies that this is a 15 general effect of inhibition of nitric oxide production. In these studies the L-NAME was given in the drinking water while the combretastatin A4 phosphate was given as an intraperitoneal injection.

Various salts of combretastatin A4 have been described for example the disodium salt, 20 the monosodium salt, the cesium salt, the calcium salt, the lithium salt, the magnesium salt, the zinc salt, the salt formed with imidazole, the salt formed with morpholine, the salt formed with piperazine, the salt formed with piperidine, the salt formed with pyrazole, the salt formed with pyridine, the salt formed with adenosine, the salt formed with cinchonine, the salt formed with quinine, the salt formed with quinidine, the salt 25 formed with glucosamine, the salt formed with tetracycline and the salt formed with verapamil (Pettit *et al.* *Anti-Cancer Drug Design* 13, 981-993, 1998). None of these has been shown to have significant therapeutic advantage over the parent phosphate.

We have found a series of novel salts with vascular damaging activity. These salts have 30 potent vascular damaging activity and are active against tumours which are resistant to vascular damaging agents such as the combretastatins. These compounds specifically damage newly-formed vascular endothelium, especially that associated with solid

tumours, without affecting the normal, established vascular endothelium of the host species. Such compounds are of use in the prophylaxis and treatment of cancers involving solid tumours and in other diseases where there is inappropriate formation of new vasculature such as diabetic retinopathy, psoriasis, rheumatoid arthritis, macular degeneration and the formation of atherosclerotic plaques. The salts are stable, soluble in aqueous media and conveniently provide a dose of a vascular damaging agent along with a dose of a nitric oxide synthase inhibitor wherein the two agents are provided in an advantageous ratio. The salts show improved vascular-damaging properties.

10 Thus according to one aspect of the invention we provide a salt comprising, as the acidic component, a compound of formula (1)

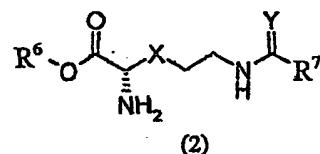


15 Wherein:

R^1, R^2 and R^3 are each independently alkyl,
 R^4 is alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl, hydroxy or halo,
20 R^5 is hydrogen, alkoxy, alkyl, alkylthio, hydroxy, phosphate or halo,

and, as the basic component, a compound of formula (2)

25



Wherein

R^6 is hydrogen or alkyl

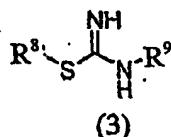
R^7 is alkyl, alkylamino, dialkylamino, nitroamino, hydrazine, mercapto or alkylthio

X is CH_2 , CH_2CH_2 , CH_2S , CH_2CH_2S

Y is NH or S

5

or, as the basic component, a compound of formula (3)

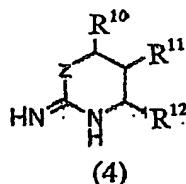


10 Wherein

R^8 is alkyl or aminoalkyl

R^9 is hydrogen, alkyl or optionally substituted phenyl

15 or, as the basic component, a compound of formula (4)



Wherein

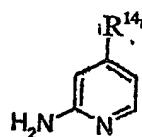
20

Z is O, S, CH_2 , CHR^{13} or a bond

R^{10} , R^{11} , R^{12} and R^{13} are each independently alkyl or hydrogen

or, as the basic component, a compound of formula (5)

25



(5)

Wherein

5

R^{14} is alkyl

and the pharmaceutically acceptable solvates and hydrates thereof.

10

The molar ratio of acidic to basic components in salts of the invention is preferably about 1:1 or about 1:2.

As used herein the term "alkyl", alone or in combinations, means a straight or
15 branched-chain alkyl group containing from one to seven, preferably a maximum of five, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl and pentyl. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy.

20 The term "halogen" means fluorine, chlorine, bromine or iodine.

An alkenyl group may be for example an olefinic group containing from two to seven carbon atoms for example methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene and t-butylene. An alkynyl group may be for example an ethynyl, 25 propynyl or butynyl group.

Optional substituents which may be present on a phenyl group may include, for example, one or more substituents selected from alkyl, haloalkyl, alkoxy, haloalkoxy, phenoxy, benzyloxy, carboxy, alkoxycarbonyl, halo and nitro.

30

Those skilled in the art will recognise that compounds of formulae (2), (3), (4) and (5) can exist in more than one tautomeric form and the invention is intended to encompass all such tautomeric forms.

- 5 Compounds of the invention can be prepared by any process known to a person skilled in the art. The salts can be prepared by standard techniques, for example by the addition of about one to about two molar equivalents of a compound of formula (2), (3), (4) or (5) in an appropriate solvent to a compound of formula (1) in an appropriate solvent. Appropriate solvents include, for example, water, alcohols such as, for
- 10 example, methanol, ethanol or isopropanol, chlorinated solvents, for example dichloromethane or chloroform, ketone solvents such as acetone or methyl ethyl ketone, ether solvents such as diethyl ether, methyl t-butyl ether, dioxane or tetrahydrofuran and nitriles such as acetonitrile and mixtures thereof. The acidic and basic components of the salt may be dissolved in the same solvent (or solvent mixture)
- 15 or in a different solvent (or solvent mixture) provided the solvents are miscible. The salts can be isolated by evaporation, crystallisation, freeze-drying or precipitation and may be purified by recrystallisation or reprecipitation.

Compounds of formulae (1) can be prepared by a number of processes as generally described hereinbelow and more specifically in the Examples hereinafter. In the general preparations described below it may be necessary to employ protecting groups which are then removed during the final stages of the synthesis. The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art. In the following process description, the symbols R¹, R², R³, R⁴ and

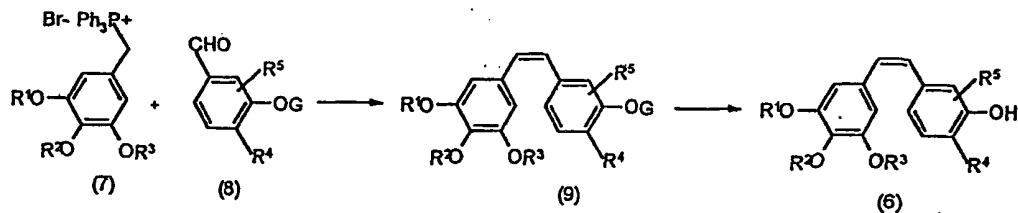
- 25 R⁵, when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated

In one general example compounds of formula (1) can be prepared by phosphorylation of phenols of formula (6) by treatment with for example di-tert-butyl

- 30 diethylphosphoramidite in the presence of a suitable catalyst for example tetrazole or in a solvent such as an ether solvent for example tetrahydrofuran at a temperature in the range -40 to 40°C, conveniently at or near room temperature, followed by treatment

with an oxidising agent for example 3-chloroperoxy benzoic acid or magnesium monoperoxyphthalate at a temperature in the range -78°C to 40°C preferably -65 to -10°C. The resulting intermediate phosphate triester is treated with an acid for example trifluoroacetic acid in a solvent such as a chlorinated solvent e.g. dichloromethane at a 5 temperature in the range -30 to 40°C conveniently at or near 0°C to give the compound of formula (1).

Compounds of formula (6) can be prepared by Wittig olefin synthesis involving reaction of a phosphonium salt of formula (7) with a strong base, for example an 10 alkylolithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a temperature of between about -100°C to about 30°C followed by treatment with an aldehyde of formula (8) in which G is a protecting group, to give an intermediate of 15 formula (9). The synthesis of compounds of formula (6) is then completed by removal of the group G. Suitable protecting groups G include trialkylsilyl, for example t-butyldimethylsilyl, and allyl. Where G is a trialkylsilyl group it may be removed, for example, by treatment with a quaternary ammonium fluoride such as tetrabutylammonium fluoride in an ether solvent such as tetrahydrofuran at a 20 temperature of about -30°C to about 40°C conveniently at or near ambient temperature. Where G is an allyl group it may be removed for example by treatment with a palladium(0) complex such as tetrakis(triphenylphosphine)Pd(0) in a solvent such as a chlorinated solvent, for example dichloromethane, at a temperature of about -40°C to about 40°C conveniently at or near ambient temperature, in the presence of an 25 allyl scavenger such as morpholine.

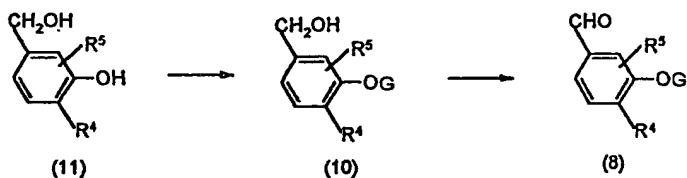


Aldehydes of formula (8) can be prepared by any process known to a person skilled in the art. In one general example an aldehyde of formula (8) can be prepared from an

alcohol of formula (10) by oxidation with a suitable oxidising agent. Suitable oxidising agents include the Dess-Martin reagent and manganese dioxide. Alcohols of formula (10) can be prepared by application of standard methods of organic synthesis including the selective protection of phenols of formula (11). Where the protecting group G is a 5 trialkylsilyl group, for example *t*-butyldimethylsilyl, alcohols of formula (10) may be prepared, for example, by treatment of a phenol of formula (11) with a strong base, for example an alkyl lithium such as *n*-butyllithium or *t*-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a 10 temperature of between about -100°C to about 40°C followed by treatment with *tert*-butylchlorodimethylsilane.

Phenols of formula (11) are either known or may be prepared from known compounds using standard methods of organic synthesis.

15



Compounds of formulae (2), (3), (4) and (5) are either known or can be prepared by methods analogous to those described in the literature.

20

Compounds according to the invention are able to destroy tumour vasculature and vasculature that has been newly formed. The ability of the compounds to act in this way may be determined by the tests described hereinafter.

25 The compounds according to the invention are thus of particular use in the prophylaxis and treatment of cancers involving solid tumours and in the prophylaxis and treatment of diseases where inappropriate angiogenesis occurs such as diabetic retinopathy, psoriasis, rheumatoid arthritis, atherosclerosis and macular degeneration.

The compounds of the invention may be administered as a sole therapy or in combination with other treatments. For the treatment of solid tumours compounds of the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors,

5 for example vinblastine, vincristine, vinorelbine, paclitaxel and docetaxel; platinum derivatives for example cisplatin and carboplatin; alkylating agents, for example melphalan, chlorambucil, busulphan, ifosfamide and cyclophosphamide; antimetabolites, for example methotrexate, 5-fluorouracil, cytosine arabinoside, gemcitabine and hydroxyurea; antitumour antibiotics for example bleomycin,

10 doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin; enzymes, for example asparaginase; topoisomerase inhibitors for example etoposide, teniposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab and trastuzumab; anti-hormones for example tamoxifen,

15 toremifene, raloxifene, droloxifene, iodoxifene, anastrozole, letrozole, vorazole, exemestane, flutamide, nilutamide and bicalutamide; anti-growth factor compounds for example EGFr tyrosine kinase inhibitors VEGFr kinase inhibitors and PDGFr tyrosine kinase inhibitors; and anti-angiogenesis agents such as angiostatin, endostatin and thalidomide. Such combination treatment may involve simultaneous or sequential

20 application of the individual components of the treatment.

For the prophylaxis and treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions selected with regard to the intended route of administration and standard pharmaceutical practice. Such

25 pharmaceutical compositions may take a form suitable for oral, buccal, nasal, topical, rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder

30 or in solution. Topical administration may be as an ointment or cream and rectal administration may be as a suppository. For parenteral injection (including intravenous,

subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

5 The dose of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician but in general daily dosages may be in the range 0.001 to 100mg/kg preferably 0.1 to 10mg/kg.

10

BIOLOGICAL ACTIVITY

The following tests were used to demonstrate the activity of compounds according to the invention.

15

Activity against tumour vasculature measured by fluorescent dye.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J 20 Cancer 57, 247-253, 1988). At least three animals were used in control and treated groups. The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 24 hours after drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 µm sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped 25 with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, 4, 47-53, 1943). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels. The salts of the invention were more efficacious than their dihydrogen phosphate parent 30 compounds.

Compound	Dose (mg/kg)	% Reduction in Vascular Volume
Example 1	50	78
Example 2	50	42
Example 5	50	86
Combretastatin A4 phosphate	100	26
(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate	100	28

Induction of tumour necrosis

5 Mice bearing either CaNT or SaS tumours were treated with the test compound and tumours excised after 24h, fixed in formalin, embedded in paraffin, sectioned and stained with haematoxylin and eosin. Sections were scored based on the estimated area of necrosis as follows:

% necrosis	score	% necrosis	score
0-10	1	51-60	6
11-20	2	61-70	7
21-30	3	71-80	8
31-40	4	81-90	9
41-50	5	91-100	10

10

Control tumours had mean scores of 2.0 (CaNT) and 1.0 (SaS). The salts of the invention were more efficacious than their dihydrogen phosphate parent compounds.

15

Compound	Tumour	Dose (mg/kg)	Score
Example 1	CaNT	50	8.7
Example 2	CaNT	50	8.7
Example 5	CaNT	50	10.0
Combretastatin A4 phosphate	CaNT	100	5.0
(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate	CaNT	100	5.3
Example 1	SaS	300	7.0
Example 2	SaS	100	7.7
Combretastatin A4 phosphate	SaS	500	1.4

The following non-limiting Example illustrates the invention:

5 EXAMPLE 1

(Z)-2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di(1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) phosphate

10 A mixture of combretastatin A4 phosphate (23mg) and L-N^G-nitroarginine methyl ester (L-NAME, 27mg) was dissolved in water, stirred 18h and freeze-dried to produce a white solid (50mg) of melting point 117-121°C.

The following were prepared in an analogous fashion to Example 1:

15 EXAMPLE 2

(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (1-carboxy-4-N'-nitroguanidinobutylammonium) hydrogen phosphate

From (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate (151mg) and L-N^G-nitroarginine (87mg) there was obtained a white solid of 20 melting point 191-194°C.

EXAMPLE 3

(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) hydrogen phosphate

5 From (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate (41mg) and L-N^G-nitroarginine methyl ester (25mg) there was obtained a white solid of melting point 89-91°C.

EXAMPLE 4

10 (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di(1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) phosphate

From (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate (41mg) and L-N^G-nitroarginine methyl ester (50mg) there was obtained a white solid of melting point 90-92°C.

15

EXAMPLE 5

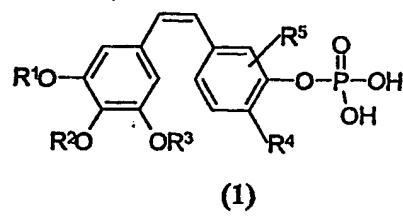
(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) hydrogen phosphate

From (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate (114mg) and 2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine (50mg) there was obtained a white solid of melting point 116-117°C.

CLAIMS:

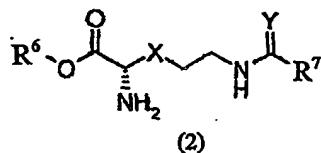
1. A salt comprising, as the acidic component, a compound of formula (1)

5



Wherein:

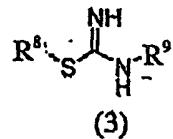
10 R^1, R^2 and R^3 are each independently alkyl,
 R^4 is alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl, hydroxy or halo,
 R^5 is hydrogen, alkoxy, alkyl, alkylthio, hydroxy, phosphate or halo,
and, as the basic component, a compound selected from the group consisting of (2) a
15 compound of formula (2)



20 Wherein

R^6 is hydrogen or alkyl
 R^7 is alkyl, alkylamino, dialkylamino, nitroamino, hydrazine, mercapto or alkylthio
X is CH_2 , CH_2CH_2 , CH_2S , CH_2CH_2S
25 Y is NH or S

or, a compound of formula (3)

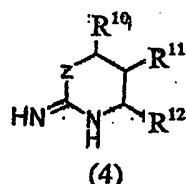


Wherein

5 R⁸ is alkyl or aminoalkyl

R⁹ is hydrogen, alkyl or optionally substituted phenyl

or, a compound of formula (4)

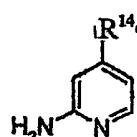


Wherein

Z is O, S, CH₂, CHR13 or a bond

15 R¹⁰, R¹¹, R¹² and R¹³ are each independently alkyl or hydrogen

or, a compound of formula (5)



20

(5)

Wherein

25 R¹⁴ is alkyl

and the pharmaceutically acceptable solvates and hydrates thereof.

5 2. A compound according to claim 1 in which the molar ratio of acidic to basic components is 1:1 or 1:2.

3. A compound according to claim 1 which is (Z)-2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di(1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) phosphate.

4. A compound according to claim 1 which is (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (1-carboxy-4-N'-nitroguanidinobutylammonium) hydrogen phosphate.

15 5. A compound according to claim 1 which is (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) hydrogen phosphate

20 6. A compound according to claim 1 which is (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di(1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) phosphate

7. A compound according to claim 1 which is (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) hydrogen phosphate.

8. A composition for the treatment of a disease involving active angiogenesis which comprises a composition containing as active agent a vascular damaging agent 30 which is a compound according to claim 1.

9. Use in the preparation of a medicament for the treatment of a disease involving active angiogenesis and containing a vascular damaging agent characterised in that the vascular damaging agent is a compound according to claim 1.

5 10. A method of treatment for a mammal having a disease involving active angiogenesis said method comprising administration of a vascular damaging agent characterised in that the vascular damaging agent is a compound according to claim 1.

10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/03668

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/12 A61K31/661 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 35150 A (ARIZONA BOARD OF REGENTS) 15 July 1999 (1999-07-15) the whole document ---	1-10
Y	BEDFORD S B ET AL: "Synthesis of water-soluble prodrugs of the cytotoxic agent combretastatin A4" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 2, 23 January 1996 (1996-01-23), pages 157-160, XP004135099 ISSN: 0960-894X the whole document ---	1-10
Y	US 5 561 122 A (GEORGE R. PETTIT) 1 October 1996 (1996-10-01) the whole document ---	1-10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
7 November 2001	14/11/2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016	Authorized officer Beslier, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/03668

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TOZER G M ET AL: "COMBREASTATIN A-4 PHOSPHATE AS A TUMOR VASCULAR-TARGETING AGENT: EFFECTS IN TUMORS AND NORMAL TISSUES" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 59, no. 7, April 1999 (1999-04), pages 1626-1634, XP000882940 ISSN: 0008-5472 the whole document	1-10
Y	PETTIT G.R. ET AL.: "Antineoplastic agents 429. Syntheses of the combrestatin A-1 and combrestatin B-1 prodrugs" ANTI-CANCER DRUG DESIGN, vol. 15, no. 3, - June 2000 (2000-06) pages 203-216, XP001030868 BASINGSTOKE, GB ISSN: 0266-9536 the whole document	1-10
P,Y	WO 00 48606 A (OXIGENE, INC.) 24 August 2000 (2000-08-24) the whole document	1-10
P,Y	WO 01 12579 A (ANGIOGENE PHARMACEUTICALS) 22 February 2001 (2001-02-22) the whole document	1-10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/03668

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9935150	A	15-07-1999	EP WO	1045853 A1 9935150 A1		25-10-2000 15-07-1999
US 5561122	A	01-10-1996	NONE			
WO 0048606	A	24-08-2000	AU WO	3597300 A 0048606 A1		04-09-2000 24-08-2000
WO 0112579	A	22-02-2001	AU WO	6458100 A 0112579 A2		13-03-2001 22-02-2001

BEST AVAILABLE COPY